Role of HLA in neural stem cell rejection using humanized mice

Grant Award Details

Role of HLA in neural stem cell rejection using humanized mice

Grant Type: Transplantation Immunology

Grant Number: RM1-01735-A

Project Objective: The goal of this project is to generate pre-clinical mouse models that have human immune systems that will be used for testing platform to evaluate the importance of matching immune system components HLAs between the human embryonic stem (hES) cell-derived neural stem cell (NSC) graft and the patient. Since mouse and human immune systems are fundamentally different, these next-generation 'humanized' mice are currently the only animal models within which to conduct our stem cell brain transplant experiments. Such models rely on immunocompromised mice as recipients for human umbilical cord blood stem cells (HSCs). These mice go on to develop a human immune system, complete with HLAs, and can subsequently be used to engraft embryonic stem cell-derived brain cells that are either HLA matched or mismatched and to monitor for graft acceptance vs. rejection.

Investigator:

Name:	Terrence Town
Institution:	Cedars-Sinai Medical Center
Type:	PI

Disease Focus: Neurological Disorders

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $1,119,385

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Role of HLA in neural stem cell rejection using humanized mice

Public Abstract:

One of the key issues in stem cell transplant biology is solving the problem of transplant rejection. Despite over three decades of research in human embryonic stem cells, little is known about the factors governing immune system tolerance to grafts derived from these cells. In order for the promise of embryonic stem cell transplantation for treatment of diseases to be realized, focused efforts must be made to overcome this formidable hurdle.

Our proposal will directly address this critically important issue by investigating the importance of matching immune system components known as human leukocyte antigens (HLA). Because mouse and human immune systems are fundamentally different, we will establish cutting-edge mouse models that have human immune systems as suitable hosts within which to conduct our stem cell brain transplant experiments. Such models rely on immunocompromised mice as recipients for human blood-derived stem cells. These mice go on to develop a human immune system, complete with HLAs, and can subsequently be used to engraft embryonic stem cell-derived brain cells that are either HLA matched or mismatched.

Due to our collective expertise in the central nervous system and animal transplantation studies for Parkinson's disease, our specific focus will be on transplanting embryonic stem cell-derived neural stem cells into brains of both healthy and Parkinson's diseased mice. We will then detect: 1) abundance of brain immune cell infiltrates, 2) production of immune molecules, and 3) numbers of brain-engrafted embryonic stem cells. Establishing this important system would allow for a predictive model of human stem cell transplant rejection based on immune system matching. We would then know how similar HLAs need to be in order to allow for acceptance stem cell grafts.

Statement of Benefit to California:

In this project, we propose to focus on the role of the human immune system in human embryonic stem cell transplant rejection. Specifically, we aim to develop cutting-edge experimental mouse models that possess human immune systems. This will allow us to determine whether immune system match versus mismatch enables embryonic stem cell brain transplant acceptance versus rejection. Further, we will explore this key problem in stem cell transplant biology both in the context of the healthy and diseased brain. Regarding neurological disease, we will focus on neural stem cell transplants for Parkinson's disease, which is one of the most common neurodegenerative diseases, second only to Alzheimer's disease. If successful, our work will pave the way toward embryonic stem cell-based treatment for this devastating neurological disorder for Californians and others.

In order to accomplish these goals, we will utilize two of the most common embryonic stem cell types, known as WiCell H1 and WiCell H9 cells. It should be noted that these particular stem cells will likely not be reauthorized for funding by the federal government due to ethical considerations. This makes our research even more important to the State of California, which would not only benefit from our work but is also in a unique position to offer funding outside of the federal government to continue studies such as these on these two important types of human embryonic stem cells.